In re Application of: Shih *et al*
Serial No.: 09/431,519
Filed: November 1, 1999

REMARKS

The time for response to the Office Action of July 22, 2003, expires on October 22, 2003. However, October 22, 2003 was a Saturday and a response filed on the next business day following a Saturday, Sunday or Federal is to be considered timely. Accordingly, it is respectfully submitted that this response is timely filed and that a fee for a one-month extension of time is due. If any additional fee is due, the Commissioner is hereby authorized to charge the same to Deposit Account No. 19-0365.

As an initial matter, Applicants wish to apologize to the Examiner for the confusion regarding the serial number, where the appeal brief was misidentified as being for U.S. Serial No. 09/260,221, rather than U.S. Serial 09/431,519.

Applicants note that the Examiner has given applicants one of two options (1) file a response to a non-final office action under 37 C.F.R. 1.111 or (2) request reinstatement of the appeal. The filing of this paper is to serve as applicants wish to respond to the non-final office action under 37 C.F.R. 1.111. Applicants thank the Examiner for his efforts in the re-opening of the prosecution of this case.

Applicants note the incorrect recitation of claim 1 where it states "comprising consisting" and apologize to the Examiner for the confusion. Applicants note that the term "comprising" was deleted in the applicants Amendment filed on January 2, 2001. Applicants have presented the Examiner the correct version of claim 1 in this version of the claim listing.

Claims 1-20 are pending in the application. Claims 1-20 stand rejected. Claims 21-42 were withdrawn by the Examiner. Applicants have amended claims 1, 8, 19 and 20. Applicants have canceled claims 21-42.

In view of the amendments and remarks, applicants respectfully submit that the application is in condition for allowance. Accordingly, applicants request reconsideration of the application, withdrawal of the rejections of record, and issuance of Notice of Allowance.

Claim Election

The Examiner stated that claims 1-42 were subject to restriction or election requirement. In response, applicants elect to pursue claims 1-20 and have cancelled claims 21-42 without prejudice to applicants' rights to pursue the cancelled subject matter in subsequent divisional applications.

Priority Issue

Applicants have amended the specification to claim priority to the provisional application (60/107,056) filed on November 11, 1998. Applicants respectfully request that priority be thereby granted to the provisional application's filing date.

Rejections under 35 U.S.C. §112 Second paragraph.

The Examiner rejected Claims 8, 11, 12, 19 and 20 under 35 U.S.C. §112, second paragraph as being indefinite. Applicants respectfully traverse this rejection.

The Examiner stated that the claims are indefinite for reciting "said anabolic agent" when the Examiner stated there are two such agents. Further, the Examiner stated that there is no estradiol benzoate in claim 1. Therefore, there is no proper antecedent basis for reciting estradiol benzoate in claim 8. The Examiner stated there is improper antecedent basis for testosterone, propionate, trenbolone, somatotrophin, salts and derivates thereof.

In response to the rejection of claim 8 for lack of proper antecedent basis, applicants have amended claim 1 to recite estradiol benzoate, testosterone, propionate, trenbolone, somatotrophin, salts and derivates thereof. Support for this amendment can be found on page 6, lines 23-28 of the specification.

With regard to claims 19 and 20, applicants have amended the claims to make it clear that the dual formulation composition, as a whole is being referred to. Therefore, applicants respectfully request the withdrawal of these rejections under §112, second paragraph.

Rejections under 35 U.S.C. §112 First paragraph.

The Examiner rejected Claims 1-20, first paragraph. The Examiner stated that the specification, while being enabling for multiple formulations, does not

reasonably provide enablement for a composition of an immediate release and controlled release agents. Applicants respectfully traverse this rejection.

In response applicants respectfully state that they have adequately enabled the claimed invention as "dual formulation." The enablement requirement of §112, first paragraph is paraphrased as such.

> The specification shall contain a written description. . . . of [the invention], in such full, clear, concise, and exact terms as to enable any person skill in the art . . . to make and use the same. . . 35 U.S.C. §112, first paragraph.

Applicants respectfully point the Examiner to the many uses of the term "dual formulation" in the specification, e.g. page 1 lines 8-9. Further, applicants respectfully suggest that one of skill in the art could read the plain language of the claims and realize that while there may be multiple ingredients, actives, excipients, etc., in the claimed invention, it is clear to one of ordinary skill in the art that the claimed invention comprises an immediate-release first formulation and a controlled-release second formulation. It is well known to one of ordinary skill in the art of pharmaceutical formulation that "the complexity of the formulation can vary from a simple aqueous solution to a complex controlled –release dosage form containing several polymeric materials." Radebaugh and Ravin, Remington: The Science and Practice of Pharmacy, 19th Ed., Chapter 83 "Preformulation", p. 1447. (see enclosed page). Applicants are to be given latitude in describing the claimed invention so long it is an enabling description. Applicants respectfully suggest that they have more than adequately described claimed invention as a dual formulation so that one of ordinary skill in the art of pharmaceutical dosage formulation will be enabled to practice the claimed invention. Therefore, applicants respectfully request the withdrawal of this rejection under §112, first paragraph.

Rejections under 35 U.S.C. §102 (b) and 35 U.S.C. §103.

The Examiner rejected Claims 1, 5 and 7-10 under 35 U.S.C. §102 (b) as being anticipated by, or in the alternative, under 35 U.S.C. §103 as being obvious under O'Callaghan. Applicants respectfully traverse this rejection.

The subcutaneous cattle pellets of O'Callaghan are described as consisting of estradiol and progesterone, estradiol and trenbolone acetate in 15 pellets.

A rejection under 35 U.S.C. §102 (b) requires that each and every element of a rejected claim be disclosed by the prior art relied upon by the Examiner for making this rejection. Since O'Callaghan does not disclose or suggest a dual formulation composition comprising an immediate-first formulation consisting essentially of an anabolic agent and a controlled-release second formulation comprising an anabolic agent and a controlled-release agent formulation wherein the anabolic agent, which may be the same or different in each formulation, is selected from the group consisting of zeranol, estradiol, estradiol benzoate, testosterone, testosterone propionate, trenbolone, somatrophin, salbutamol, progesterone, trenbolone acetate, salts and derivatives and combinations thereof. Accordingly, applicants respectfully request reconsideration and withdrawal of this rejection under 102(b).

Applicants respectfully suggest that the claimed invention, is NOT obvious in light of O'Callaghan for the following reasons. Applicants respectfully suggest that there is no teaching O'Callaghan to suggest to or motivate one or ordinary skill in the art to practice the applicants' claimed invention in light of the select number of anabolic agents claimed by the applicants to be used in the applicants' claimed dual formulation.

Therefore, applicants respectfully request the withdrawal of this rejection under §103.

The Examiner rejected Claims 1-20 under 35 U.S.C. §103 as being obvious under O'Callaghan, in view of Nessel, Stevens and Dick. Applicants respectfully traverse this rejection.

As stated above, there is no teaching in O'Callaghan to suggest or motivate one or ordinary skill in the art to practice the applicants' claimed invention of a dual formulation composition wherein the anabolic agent is zeranol, estradiol, estradiol benzoate, testosterone, testosterone propionate, trenbolone, somatrophin, salbutamol, progesterone, trenbolone acetate, salts and derivatives and combinations thereof. Further none of the cited references, Nessel, Stevens or Dick, teach the claimed invention's combination of anabolic agents in the claimed dual formulation composition. Nessel, Stevens and Dick all merely demonstrate the

basic concepts of using pharmaceutical excipients as potential means of controlling the release of active drug compounds. None of the additional references disclose or suggest any teaching or motivation, that can be combined with O'Callaghan, in order to render obvious the applicants' dual formulation composition comprising an immediate-first formulation consisting essentially of an anabolic agent and a controlled-release second formulation comprising an anabolic agent and a controlled-release agent formulation wherein the anabolic agent, which may be the same or different in each formulation, is zeranol, estradiol, testosterone, salbutamol, progesterone, trenbolone acetate, or combinations thereof. Applicants, therefore, respectfully request withdrawal of this rejection under 35 U.S.C. §103.

The Examiner rejected Claims 1-4, 7-9, 13-15 and 20 under 35 U.S.C. §103 as being obvious under Ivy. Applicants respectfully traverse this rejection.

The Ivy formulation is a mixture of a growth-promoting hormone *and* a zearalin. See Col. 1, lines 19-21. The present invention differs from Ivy, because the present invention is a dual formulation composition comprising an immediate-first formulation consisting essentially of an anabolic agent and a controlled-release second formulation comprising an anabolic agent and a controlled-release agent formulation wherein the anabolic agent, which may be the same or different in each formulation, is selected from the group consisting of zeranol, estradiol, estradiol benzoate, testosterone, testosterone propionate, trenbolone, somatrophin, salbutamol, progesterone, trenbolone acetate, salts and derivatives and combinations thereof. Ivy requires using only growth hormone and zearalin. Ivy does not disclose or suggest using an anabolic agent selected from the group consisting of zeranol, estradiol, testosterone, salbutamol, progesterone, trenbolone acetate, or combinations thereof. Accordingly, Applicants, therefore, respectfully request withdrawal of this rejection.

The Examiner rejected Claims 1-9, 11-13, 16, 17 and 20 under 35 U.S.C. §102(b) as being anticipated by, or in the alternative, under 35 U.S.C. §103(b) as being obvious under Deasy. Applicants respectfully traverse this rejection. The present invention is not suggested or disclosed in Deasy.

The Deasy formulation requires that each shaped piece of the multi-component implant contain biologically degradable copolymers of lactic acid and

glycolic acid with a lactide to glycolide weight ratio of 90:10 to 60:40. See Column 1, lines 50-55 and Claim 1.

In contrast, the present invention is a dual formulation composition comprising an immediate-first formulation consisting essentially of an anabolic agent and a controlled-release second formulation comprising an anabolic agent and a controlled-release agent formulation wherein the anabolic agent, which may be the same or different in each formulation, is selected from the group consisting of zeranol, estradiol, estradiol benzoate, testosterone, testosterone propionate, trenbolone, somatrophin, salbutamol, progesterone, trenbolone acetate, salts and derivatives and combinations thereof. Because the immediate-release first formulation consists essentially of an anabolic agent, it cannot contain biologically degradable copolymers of lactic acid and glycolic acid with a lactide to glycolide weight ratio of 90:10 to 60:40. A significant difference between the controlled release formulation and the immediate release formulation of the present invention is that the controlled-release formulation has a polymer matrix, such as poly(D,L-Lactide-co-glycolide) to control the release of the anabolic agent, and the immediate-release formulation does not have a polymer matrix to control the release of the anabolic agent. (See page 7 of specification). To include the biologically degradable copolymers of lactic acid and glycolic acid with a lactide to glycolide weight ratio of 90:10 to 60:40 in the immediate release formulation of the present invention, as Deasy would require, would change the essential characteristics of the immediate release formulation. Furthermore, Deasy does not disclose or suggest using an anabolic agent selected from the group consisting of zeranol, estradiol, estradiol benzoate, testosterone, testosterone propionate, trenbolone, somatrophin, salbutamol, progesterone, trenbolone acetate, salts and derivatives and combinations thereof. Accordingly, the present invention is not anticipated by the Deasy reference.

A rejection under 35 U.S.C. §102 (b) requires that each and every element of a rejected claim be disclosed by the prior art relied upon by the Examiner for making this rejection. Since Deasy does not disclose or suggest a dual formulation composition comprising an immediate-first formulation consisting essentially of an anabolic agent and a controlled-release second formulation comprising an anabolic

agent and a controlled-release agent formulation wherein the anabolic agent, which may be the same or different in each formulation, is selected from the group consisting of zeranol, estradiol, estradiol benzoate, testosterone, testosterone propionate, trenbolone, somatrophin, salbutamol, progesterone, trenbolone acetate, salts and derivatives and combinations thereof. Accordingly, applicants respectfully request reconsideration and withdrawal of this rejection.

Further, applicants respectfully suggest that the claimed invention is NOT obvious in light of Deasy for the following reasons. As stated above, the biologically degradable copolymers of lactic acid and glycolic acid with a lactide to glycolide weight ratio of 90:10 to 60:40 in the immediate release formulation of the present invention, as Deasy would require, would change the essential characteristics of the immediate release formulation. Applicants respectfully state that the biologically degradable copolymers of lactic acid and glycolic acid, as required by Deasy, teaches AWAY from the applicants' claimed invention. Applicants respectfully suggest that there is no teaching Lewis to suggest to or motivate one or ordinary skill in the art to practice the applicants' claimed invention in light of the select number of anabolic agents claimed by the applicants to be used in the applicants' claimed dual formulation. Applicants respectfully request the withdrawal of this rejection under §103.

The Examiner rejected claims 1-13, 16, 17 and 19 under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative 35 U.S.C. §103(a) as being obvious under Lewis. Applicants respectfully traverse this rejection.

Lewis discloses biodegradable coating formulations for coating sustained-release drug implants, wherein the formulation comprises a water-soluble pore-forming agent mixed with water insoluble polymers. See Column 6, lines 25-32.

In contrast, the present invention is a dual formulation composition comprising an immediate-first formulation consisting essentially of an anabolic agent and a controlled-release second formulation comprising an anabolic agent and a controlled-release agent formulation wherein the anabolic agent, which may be the same or different in each formulation, is selected from the group consisting of zeranol, estradiol, estradiol benzoate, testosterone, testosterone propionate, trenbolone, somatrophin, salbutamol, progesterone, trenbolone acetate, salts and

derivatives and combinations thereof. Because the immediate-release first formulation consists essentially of an anabolic agent, it cannot contain a water-soluble pore-forming agent mixed with water insoluble polymers. As stated above, a significant difference between the controlled release formulation and the immediate release formulation of the present invention is that the controlled-release formulation has a polymer matrix, such as poly(D,L-Lactide-co-glycolide) to control the release of the anabolic agent, and the immediate-release formulation does not have a polymer matrix to control the release of the anabolic agent. (See page 7 of specification). To include the water-soluble pore-forming agent mixed with water insoluble polymers in the immediate-release formulation of the present invention, as Lewis would require, would change the essential characteristics of the immediate release formulation. Furthermore, Lewis does not disclose or suggest using an anabolic agent selected from the group consisting of zeranol, estradiol, estradiol benzoate, testosterone, testosterone propionate, trenbolone, somatrophin, salbutamol, progesterone, trenbolone acetate, salts and derivatives and combinations thereof. Accordingly, the present invention is not anticipated by the Lewis reference. Applicants respectfully request the withdrawal of this rejection §102.

Further, applicants respectfully suggest that the claimed invention, is NOT obvious in light of Lewis for the following reasons. As stated above, the water soluble pore-forming agent mixed with water insoluble polymers in the immediate-release formulation of the present invention, as Lewis would require, would change the essential characteristics of the immediate release formulation. Applicants respectfully state that this water-soluble pore-forming agent mixed water insoluble polymers, as required by Lewis, teaches AWAY from the applicants' claimed invention. Applicants respectfully suggest that there is no teaching Lewis to suggest to or motivate one or ordinary skill in the art to practice the applicants' claimed invention in light of the select number of anabolic agents claimed by the applicants to be used in the applicants' claimed dual formulation. Applicants respectfully request the withdrawal of this rejection under §103.

Claims 1-6, 8, 13-16, 19 and 20 have been rejected by the Examiner under 35 U.S.C. §102(b) as being anticipated by Sivaramarkishnan ('572). Applicants respectfully traverse this rejection.

The '572 patent discloses a controlled release delivery device for implantation in an animal whereby a macromolecular protein is administered over a prolonged period of time, comprising a plurality of beads containing said protein in a ruptural wax shell and a water-soluble outer capsule surrounding said beads. See claim 1 of the '572 patent.

In contrast, the present invention is a dual formulation composition comprising an immediate-first formulation consisting essentially of an anabolic agent and a controlled-release second formulation comprising an anabolic agent and a controlled-release agent formulation wherein the anabolic agent, which may be the same or different in each formulation, is selected from the groups consisting of zeranol, estradiol, estradiol benzoate, testosterone, testosterone propionate, trenbolone, somatrophin, salbutamol, progesterone, trenbolone acetate, salts and derivatives and combinations thereof.

A rejection under 35 U.S.C. §102 (b) requires that each and every element of a rejected claim be disclosed by the prior art relied upon by the Examiner for making this rejection. Since the '572 patent does not disclose or suggest a dual formulation composition comprising an immediate-release first formulation consisting essentially of an anabolic agent and a controlled-release second formulation comprising an anabolic agent and a controlled-release agent formulation wherein the anabolic agent, which may be the same or different in each formulation, is selected from the group consisting of zeranol, estradiol, estradiol benzoate, testosterone, testosterone propionate, trenbolone, somatrophin, salbutamol, progesterone, trenbolone acetate, salts and derivatives and combinations thereof. Further, the '572 patent requires the delivery of its active ingredient through a plurality of beadlets, a rupturable wax shell and a water-soluble outer capsule, elements not present in the claimed invention.

Accordingly, the present invention is not anticipated by the '572 patent. Applicants respectfully request the withdrawal of this rejection §102.

In summary, the instant invention discloses a dual formulation, only one of which consists essentially of an anabolic agent, and the other which comprises an

anabolic agent and a controlled-release agent. None of the references cited by the Examiner, alone or in combination, disclose or suggest the present invention. Applicants, therefore, believe that whether used alone or in combination, the references cited by the Examiner do not anticipate or render the present invention obvious.

Applicants believe that Claims 1-20 are in condition for allowance, and such action is earnestly requested. If the Examiner has any questions, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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CHAPTER 83

preformulation

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The intelligent selection of new potential drug compounds from the discovery process, and their formulation into dosage forms with high and consistent bioavailability, is more important than ever in the pharmaceutical industry. Reasons for this importance include the time and expense required to discover and develop new drugs; the cost of drug substances; more drugs with solubility and bioavailability problems; the advent of highly potent biotechnology-derived proteins and peptides; lot-to-lot changes in the physical-chemical properties of drug substance and multisourcing of drug substance and drug product.

Statistics indicate that the odds of a new compound synthesized in the discovery process becoming a commercially viable drug product is less than 1 in 10,000. The reasons for these poor odds are many and include those of scientific and marketing origins. Included in the reasons is the selection of compounds for development that had unsuitable physical-chemical properties such as instability or insolubility that ultimately led to poor bioavailability or efficacy in human clinical studies. Solutions for these problems often are found in the preformulation process where the physical, chemical and mechanical properties of drug substances are determined.

The stage in the research and development process at which preformulation begins can greatly affect the odds of a new compound becoming a commercially viable drug product. In general, the sooner preformulation data is available, the earlier decisions can be made about the nature of the physical-chemical properties and how these might impact on the development potential of a new drug candidate. For example, when the preformulation scientist works closely with discovery scientists, preformulation data along with biological data can be used to select from a group of compounds, the best compound for future development. It is all too common that new compounds are chosen for development without adequate preformulation data. Hence, problems with stability, solubility and bioavailability occur in the dosage-form development process that could have been prevented or modified had preformulation data been part of the compound selection process.

The bioequivalency of multisource pharmaceutical products continues to receive great attention from practitioners and regulatory authorities alike. It is well documented that the bioavailability of certain drugs is very susceptible to the physical-chemical properties of the drug substance and the process and composition of the formulation. As a result, the efficacy of the formulations can vary dramatically. Even though this does not occur with all drugs, the manner in which the information has been reported by scientists often appears unclear to the practitioner. The information also has been misinterpreted differently depending on the motivation, viewpoint and attitude of the interpreter.

To optimize the performance of drug products, it is necessary to have a complete understanding of the physical-chemical and mechanical properties of drug substances prior to formulating them into drug products. The development of an optimum formulation is not an easy task, and many factors readily influence formulation properties. Drug substances rarely are administered as pure chemical entities, and are almost always given in a formulation containing excipients. The complexity of the formulation can vary from a simple aqueous solution to a complex controlled-release dosage form containing several polymeric materials. Sometimes the degree of complexity is determined by patent motivation, but more often it is determined by the properties that are expected from or built into the dosage form and by the resulting composition that is required to achieve these qualities.

The high degree of uniformity, physiological availability and therapeutic quality expected of modern medicinal products usually are the result of considerable effort and expertise on the part of the formulating pharmacist. These qualities are attained by careful selection and control of the quality of the various ingredients employed, appropriate manufacturing according to well-defined processes and, most importantly, adequate consideration of the many variables that may influence the composition, stability and utility of the product. In dealing with the formulation of new products it has become necessary to apply the best research methods and tools in order to develop, produce and control the potent, stable and effective dosage forms which make up our modern medical armamentarium.

The pharmaceutical formulator has a need for specialized areas of science in order to acquire and understand scientific information about the drug substance that is necessary to develop an optimum dosage form. The pharmaceutical industry no longer can rely only on past experience or empirical thinking to formulate dosage forms. Industry does not have the time or resources to operate by empirically putting dozens of formulations on a stability-testing schedule and waiting to see which were the most stable. Nor does it have the time or resources to test all these formulations for optimum bioavailability. In short, as much information must be acquired about the drug substance very early in its development. This requires an interdisciplinary approach during the preformulation exercise. Figure 1 shows how the development of a drug requires a multidisciplinary approach involving basic science during the preformulation phase followed by applied science during the development phase.

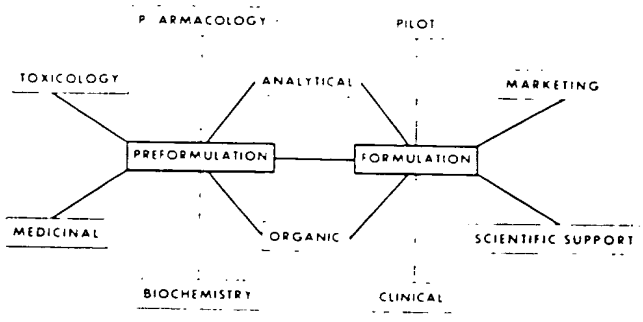

Fig 1. The wheels of product development.